Diabetic Nephropathy—A Review of the Natural History, Burden, Risk Factors and Treatment

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This paper reviews the natural history, burden, risk factors, and treatment of diabetic nephropathy.

The earliest clinical evidence of diabetic nephropathy is microalbuminuria. Progression from microalbuminuria to overt nephropathy occurs in 20–40% within a 10-year period with approximately 20% of these patients progressing to end-stage renal disease. End-stage renal disease develops in 50% of type-1 diabetes patients with overt nephropathy within 10 years and in more than 75% by 20 years in the absence of treatment. In type-2 diabetes, a greater proportion of patients have microalbuminuria and overt nephropathy at or shortly after diagnosis of diabetes.

The incidence of diabetes is increasing worldwide, with subsequent increase in the incidence of diabetic nephropathy. The risk factors identified in the development of DN from longitudinal and cross-sectional studies include race, genetic susceptibility, hypertension, hyperglycemia, hyperfiltration, smoking, advanced age, male sex, and high-protein diet.

Treatment interventions in diabetic nephropathy include glycemic control, treatment of hypertension, hyperlipidemia, cessation of smoking, protein restriction, and renal replacement therapy. Multifactorial approach includes combined therapy targeting hyperglycemia, hypertension, microalbuminuria, and dyslipidemia.

Key words: diabetic nephropathy ■ burden ■ risk factors ■ treatment

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INTRODUCTION

Diabetic nephropathy (DN) refers to a characteristic set of structural and functional kidney abnormalities in patients with diabetes.[1] The structural abnormalities include hypertrophy of the kidney, increase in glomerular basement membrane thickness, nodular and diffuse glomerulosclerosis, tubular atrophy, and interstitial fibrosis.[2,3] The functional alterations include an early increase in glomerular filtration rate with intraglomerular hypertension, subsequent proteinuria, systemic hypertension, and eventual loss of renal function.[4,5] Mogensen et al. suggested that DN can be divided into five stages: 1) early hypertrophy stage characterized by increase in renal plasma flow and GFR; 2) silent stage, which is associated with subtle morphological changes, including thickening of the glomerular basement membrane, glomerular hypertrophy, mesangial, and tubulointerstitial expansion; 3) incipient DN characterized by microalbuminuria with likely onset of hypertension; 4) overt DN characterized by dipstick-positive proteinuria; and 5) end-stage renal disease (ESRD) with uremia.[6] However, it is often difficult to document these various stages in a diabetic patient in clinical practice because of confounding factors, such as blood pressure medications, which modify the natural course of DN.[7]

The aim of this review paper is to update knowledge on DN, vis à vis its burden, risk factors, natural history, and strategies to counteract the condition.

NATURAL HISTORY OF DN

The earliest clinical evidence of DN is microalbuminuria defined as urinary albumin excretion of 30–299 mg/24 hours in a 24-hour urinary collection, 20–199 μg/min in a timed urine collection, or 30–299 μg/mg creatinine in a spot urine collection on at least two occasions within a three-to-six month period.[8,9] In the absence of specific interventions, about 80% of patients with type-1 diabetes with sustained microalbuminuria progress to the stage of overt nephropathy or clinical microalbuminuria

(defined as urinary albumin excretion >300 mg/24 hours, >200 mg/min in a timed collection, or >300 μg/mg creatinine in a spot urine) over a period of 10 to 15 years.[8-10] However, in patients who develop microalbuminuria late in the course of the disease (i.e., after more than 15 to 29 years), the risk of developing overt renal disease is only about 1% per year. ESRD develops in 50% of type-1 diabetes patients with overt nephropathy within 10 years and in more than 75% by 20 years in the absence of treatment.[8]

A greater proportion of patients with type-2 diabetes compared with type-1 diabetes have microalbuminuria and overt nephropathy at or shortly after diagnosis of diabetes.[8] This is because the disease may have been present for several years before the diagnosis is made.[8] In addition, concomitant presence of hypertension at the time of diagnosis also contributes to the high prevalence of microalbuminuria in type-2 diabetes. Progression from microalbuminuria to overt nephropathy occurs in 20–40% of Caucasians within a 10-year period, with approximately 20% of those with overt nephropathy progressing to ESRD over a period of 20 years.[8,9]

THE BURDEN OF DN

The incidence of DN has increased by 150% in the past 10 years in the United States with a similar trend in Europe and Japan.[11,12] Diabetes mellitus is now the most common cause ESRD in the United States and Japan, accounting for 45% and 37% of cases respectively.[13] This is due to an increase in the prevalence of diabetes mellitus, particularly type-2;[14] an increase in the life span of patients with diabetes; and acceptance of patients with diabetic ESRD for treatments in ESRD programs where formerly they had been excluded.[8,15] A similar trend of increase in the proportion of chronic renal failure attributed to diabetes has also been observed in developing countries. In Southwest Nigeria, diabetes mellitus accounted for 2% of patients with chronic renal failure in 1989.[16] By 2002, the figure had risen to 5%.[17] Diabetes mellitus accounted for 21% of patients on chronic dialysis in Libya,[18] 9% of chronic renal failure in Sudan,[19] and 20.3% of the patients accepted for renal replacement therapy between 1990 and 1996 in Tunisia.[20]

Patients with diabetes undergoing dialysis have a 22% and 15% higher mortality at one year and five years, respectively, when compared with patients without diabetes,[9] and specifically the first-year mortality of patients with type-2 diabetes who require dialysis exceeds 20%.[21] The average survival on dialysis in the United States is four-to-five years, with death generally resulting from cardiovascular disease or infection,[21] while in Germany the five-year survival is only 5% among patients with type-2 diabetes undergoing dialysis.[22] Type-2 diabetic patients have a cardiovascular risk equivalent to nondiabetic individuals with a previous myocardial infarction.[23] With the onset of DN, this risk is further increased.[24] Renal failure accounted for 50% of the mortalities in patients with type-1 diabetes over a 10-year period in Soweto, and 8% of deaths in patients with diabetes in Sudan.[25,26] The estimated annual cost for dialysis in a diabetic patient in United States in 1998 was $12,000 more than that of a nondiabetic patient.[8,27] In 1997, the cost of treatment of patients with diabetic ESRD in the United States was in excess of $15.6 billion.[8] By the year 2010, there will be an estimated 660,000 patients in the United States receiving dialysis with a potential cost of $30 billion.[21]

The risk factors identified in the development of DN from longitudinal and cross-sectional studies include race, genetic susceptibility, elevated blood pressure, increased blood sugar, hyperfiltration, smoking, and possibly, male gender, dyslipidemia, and age[10,28-33] (Table 1).

Race

The incidence and severity of DN are increased in blacks, Mexican Americans, Pima Indians, and Hispanics compared with Caucasians[10,34] (Table 1). Even after adjusting for confounding factors such as lower socioeconomic status and increased incidence of hypertension in blacks, there is still a 4.8 times greater risk of ESRD in blacks compared to Caucasians.[35]

Genetic Predisposition

Genetic predisposition to DN is suggested by the observation that the diabetic sibling of a patient with DN has a three-fold greater risk of developing nephropathy than the diabetic sibling of a diabetic without nephropathy.[27] Seaquist et al. reported that 83% of type-2 diabetic siblings of probands with DN have evidence of renal disease compared with only 17% of siblings of probands without nephropathy.[36] In a study in Pima Indian families in which two successive generations had type-2 diabetes, the likelihood of the offspring developing overt nephropa-

Table 1. Diabetic Nephropathy Risk Factors

- Genetic susceptibility
- Race
- Elevated blood pressure
- Elevated blood sugar
- Hyperfiltration
- Age
- Male gender
- Dyslipidemia

thy was 14% if no parent had proteinuria, 23% if one parent had proteinuria, and 46% if both parents had proteinuria.[29] In patients with type-2 diabetes, the DD (homozygous deletion genotype) polymorphism of the angiotensin converting enzyme (ACE) genotype has been associated with an increased risk for the development of DN, more severe proteinuria, a greater likelihood of progressive renal failure, and an enhanced mortality on dialysis.[37-39] However, among Caucasians, the presence of the insertion or deletion polymorphism of the ACE gene is not a major predictor of DN.[38] In type-1 diabetes, homozygosity for the Z-2 allele of the aldose reductase gene has been associated with DN.[40] The β_3 subunit of the G protein at position 825 ($G\beta_3$ 825 T) allele is more frequent among patients with type-2 diabetes, with progression to ESRD, than among nondiabetic patients.[41]

Elevated Blood Pressure

The presence of hypertension in the diabetic population is 1.5- to three times higher than in a nondiabetic, age-matched group.[42,43] An association between subsequent development of nephropathy and higher systemic pressures, particularly if in the hypertensive range, has been observed in prospective studies.[44,45] In addition, an abnormal circadian blood pressure profile has been found to strongly correlate with the presence of albuminuria and is a predictor of renal and cardiovascular events in type-2 diabetes.[46]

Increased Blood Sugar Level

DN is more likely to develop in patients with lesser degrees of glycemic control.[47] This is supported by studies, which showed that the risk of development and progression of albuminuria could be substantially reduced by improving glycemic control.[48-50]

Smoking

Smoking causes a substantial increase in the risk of both micro- and macrovascular diseases in diabetes.[51] Smoking is an independent risk factor for the development of DN and is associated with an accelerated loss of renal function, an increased risk for ESRD, and decreased survival on commencement of dialysis.[52-54]

Male Gender

Male gender has been associated with the development of nephropathy in diabetes in many studies. Gall et al., in a prospective observational study involving 176 patients with type-2 diabetes, found that males had a 2.6 times greater risk of developing incipient or overt nephropathy.

Dyslipidemia

Many observational studies suggest that lipids may play a role in the development and progression of glomerular injury. Ravid et al.[31] fount that the level of cholesterol both at onset and after a five-year follow-up period was positively related with the subsequent increase in urinary albumin excretion in microalbuminuric patients with type-2 diabetes. Gall et al.[30] found that total serum cholesterol was significantly associated with development of abnormally increased urinary albumin excretion. Klein et al.,[54] in a study of type-1 individuals, found that higher total serum cholesterol and lower HDL cholesterol were associated with incidence of renal insufficiency.

Age

Gall et al.[30] found that increasing age was significantly associated with abnormally increased urinary albumin excretion rate in both univariate and multivariate analysis. However, Klein et al.[54] found that younger age at diagnosis was significantly associated with a decrease in the estimated annual creatinine clearance in patients with type-1 diabetes.

TREATMENT OF DN

Interventions that have been found useful in preventing or retarding the progression of DN include strict glycemic control, strict blood pressure control, cessation of smoking, and possibly control of hyperlipidemia and restriction of protein intake. Patients who develop ESRD will require renal replacement therapy. (Table 2).

Glycemic Control

Studies have shown that strict glycemic control delays the development of microalbuminuria, stabilizes or reduces protein excretion in patients with microalbuminuria and overt proteinuria, and slows the rate of progression to chronic renal failure.[48-50] The Diabetes Control and Complications Trial (DCCT) compared conventional (mean achieved glycosylated hemoglobin [HbA_{IC}] 9.1%) with intensive treatment (mean achieved HbA_{IC} 7.3%) in 1,441

Table 2. Treatment Interventions in Diabetic Nephropathy

- Glycemic control
- Treatment of hypertension
- Cessation of smoking
- Protein restriction
- Control of dyslipidemia
- Renal replacement therapy
- Multifactorial approach
  - Combined therapy targeting hyperglycaemia, hypertension, and dyslipidemia.

type-1 diabetic patients. In the combined cohorts, intensive treatments reduced the development of microalbuminuria and clinical albuminuria by 39% and 56%, respectively.[55]

The long-term impact of intensive treatment on microvascular complications was studied in the succeeding observational follow-up of the DCCT cohort—the Epidemiology of Diabetes Interventions and Complications (EDIC) study.[56] A total of 1,375 of the DCCT subjects volunteered to participate in the EDIC study. The mean HbA_{IC} levels of the two former randomized treatment groups continued to narrow and became statistically nonsignificant by five years (8.1% vs. 8.2%, P=0.09). After four years of the EDIC study, the development of microalbuminuria and albuminuria in those without these nephropathic outcomes at the DCCT closeout were reduced by 53% and 86%, respectively.[56] At the fifth- and sixth-year examinations of the 1,298 EDIC study participants, the prevalence of microalbuminuria in those without it at DCCT closeout remains less in the former intensive treatment group than conventional treatment group (4.5% vs. 12.3%, risk reduction of 67%, P<0.001).[57] In subjects with either normal albuminuria or microalbuminuria at DCCT closeout, the risk reduction in subsequent development of clinical albuminuria in the former intensive group was 84% (P<0.001). Furthermore, by six years in EDIC, the prevalence of hypertension in the conventional group has become significantly greater than in the intensive group (33% vs. 25%, P<0.001), despite the fact that there was no treatment group difference in the prevalence of hypertension at the end of the DCCT (12% in the conventional arm vs. 11% in the intensive group).[57] Thus, the overall DCCT/EDIC results show that the microvascular effects of hyperglycemia persist for a considerable period after glucose levels have decreased and the benefits of intensive therapy are long-lasting and persist beyond the period of shortest intervention.[57]

Ohkubo et al.,[58] in a randomized study, compared intensive control using three or more injections per day with conventional therapy using one or two injections per day in 110 nonobese subjects with type-2 diabetes. Intensive treatment resulted in a lower rate of new or progressive nephropathy over a period of six years than did conventional therapy (7.7% vs. 28%).

The American Diabetes Association recommends that treatment aim at achieving target pre-prandial glucose of 80–120 mg/dL (whole blood) or 90–130 mg/dL (plasma); bedtime glucose of 100–140 mg/dL (whole blood) or 110–150 mg/dL (plasma), and HbA_{IC} of <7%.[59] Target blood sugar levels can be achieved using oral hypoglycemic agents, insulin, or a combination of both. Recently, rosiglitazone was shown to significantly reduce albumin-creatinine ratio at week 52 compared to glyburide in an open-label clinical study, though both treatment groups showed reduced albumin-creatinine ratio at week 28.[60] This effect was independent of the changes in plasma glucose or HbA_{IC} and is thought to be due to improvement in vascular integrity and tone. Thus, the use of rosiglitazone (and possibly, the thiazolidinediones in general) may offer additional benefit.

Blood Pressure Control

Both systolic and diastolic hypertension markedly accelerate the progression of DN, and aggressive antihypertensive management has been shown to decrease the rate of fall of glomerular filtration rate, increase the median life expectancy, and reduce the need for dialysis and transplantation.[61-65] The primary goal of therapy for nonpregnant patients with diabetes aged >18 years is to reduce blood pressure below 130/80 mmHg for patients with proteinuria <1 g/day, and <125/75 mmHg for patients who have ≥1 g/day of proteinuria.[42,43,66,67]

ACE inhibitors are recommended as first-line therapy for patients with type-1 and type-2 diabetes.[42,43] Angiotensin-II receptor blockers are now recommended as first-line therapy for patients with type-2 diabetes by the American Diabetes Association.[43] Both classes of drugs reduce the risk of the development or progression of overt nephropathy.[68-70] In addition, ACE inhibitors have a well-documented cardioprotective effect in diabetic patients with known ischemic heart disease, particularly those with congestive heart failure or postmyocardial infarction.[42,43,65] These benefits of ACE inhibitors and angiotensin-II receptor blockers appear partly independent of their antihypertensive effect. The diabetes substudy of the Heart Outcomes Prevention Evaluation study showed that at similar blood pressures, ramipril resulted in a 24% greater decrease in the rate of progression to overt nephropathy than did placebo in patients with type-2 diabetes and without or with microalbuminuria.[71] In the Reduction in Endpoints in noninsulin-dependent diabetes mellitus with the Angiotensin-II antagonist losartan study, treatment with losartan combined with conventional antihypertensive therapy (excluding ACE inhibitors and angiotensin-II receptor blockers) was compared with conventional treatment alone.[72] The risk of the primary end point, a composite of a doubling of the serum creatinine, ESRD, or death from any cause was reduced by 16% in the losartan arm. In addition, urinary protein excretion, the risk of doubling of serum creatinine, the risk of ESRD, and the combined risk of ESRD or death were decreased by 34% (P<0.001), 25% (P=0.006), 28% (P=0.002) and 20% (P=0.01), respectively, in the losartan arm compared

with the placebo group.[72]

Other agents that can be used to lower blood pressure include ß blockers, calcium channel blockers, and diuretics. In the United Kingdom Prospective Diabetes Study, atenolol showed beneficial effects comparable to captopril on diabetes-related mortality and microvascular complications in patients with type-2 diabetes.[73,74] Beta-blockers have been shown to reduce mortality following myocardial infarction, and the absolute benefit of a given relative reduction is greater in diabetics compared to nondiabetics due to higher mortality from myocardial infarction in patients with diabetes.[75] A recent analysis of the literature indicates that $ß_1$ selective agents do not significantly affect glucose metabolism nor prolong hypoglycemia or mask hypoglycemic symptoms.[76]

The nondihydropyridine calcium channel blockers have been shown to lower protein excretion in patients with diabetes.[77,78] Their antiproteinuric effect may be due to reduction in intraglomerular pressure, reduction in glomerular hypertrophy, and improved glomerular size (diltiazem).[79] The dihydropyridine calcium channel blockers have a variable effect on protein excretion ranging from increased protein excretion to no effect to a fall in protein excretion in various studies.[80-83]

Thiazides have been shown to decrease cardiovascular morbidity and to reduce the risk of stroke and congestive cardiac failure in trials, including subjects with mild-to-moderate hypertension. In diuretic-based therapy, a low-dose thiazide diuretic has been shown to reduce the cardiovascular event rate by 34% compared to placebo; the absolute risk reduction is twice as great for diabetic subjects compared to nondiabetic.[84] The effect of thiazide diuretics on the progression of early or advanced DN has not been studied in large clinical trials. Thiazides at low doses do not significantly decrease insulin sensitivity and are associated with very low risk of side-effects, such as hypokalemia, hyperuricemia, hyponatremia, or hypercalcemia.[42,43] Thiazides may not be effective in subjects who have significantly reduced renal function (that is, GFR <60 ml/min per $1.73m^2$). Loop diuretics can be used in such patients with decreased renal function.

There are studies suggesting that dual blockade of renin-angiotensin system using a combination of ACE inhibitor and angiotensin-II receptor blocker in patients with nephropathy is superior to the use of either drug alone.[85-88] Rossing et al.,[87] in a double-blind cross-over study, investigated the effects of candesartan and placebo in type-2 diabetes patients with nephropathy who were responding insufficiently to previous antihypertensive therapy, including ACE inhibitors in recommended doses (lisinopril/enalapril 20 mg daily, captopril 100 mg daily). The addition of candesartan to usual antihypertensive therapy induced a mean reduction in albuminuria, fractional clearance of albumin and of IgG of 25% (P=0.036), 35% (P=0.016), and 32% (P=0.046), respectively. In addition, there was a reduction in 24-hour systolic blood pressure of 10 mmHg (P=0.019) and a mean reduction in glomerular filtration rate of 5 mL/min per $1.73m^2$ (P=0.045). Treatment with benazepril and valsartan in type-1 diabetes patients with DN was found to induce additional reduction in albuminuria of 43%, reduce systolic blood pressure by 6 mmHg and 7 mmHg compared with benazepril and valsartan monotherapy, respectively, and reduces diastolic BP by 7 mmHg compared with both monotherapies. The antiproteinuric effects of inhibitors of the renin angiotensin system are increased by sodium restriction and by concomitant administration of diuretics or nondihydropyridine calcium channel blockers.[42,43]

Cessation of Smoking

Loss of renal function is slower in those who stopped smoking. Cessation of smoking alone may reduce the risk of progression by 30% in patients with type-2 diabetes.[89]

Protein Restriction

The role of dietary protein restriction in chronic renal disease is controversial.[90-91] However, restriction of protein (0.6 g of protein/kg body weight per day) and phosphorus (500 mg to 1 g of phosphorus per day) was shown to reduce the decline in glomerular filtration rate, lower blood pressure, and stabilize renal function compared with a higher intake of protein and phosphorus in a randomized trial involving patients with type-1 diabetes and overt nephropathy.[92] In addition, restriction of protein intake to 0.8 g/kg body weight per day, which is consistent with the recommended daily allowance, has been shown to reduce the rate of progression to ESRD in patients with type-1 diabetes in another study.[93] The National Kidney Foundation recommends that patients with GFR <29 mL/min per $1.73m^2$ should have a daily protein intake of 0.6 g/kg body weight.[94]

Hyperlipidemia

There is suggestion that elevation in lipid levels may contribute to the development of glomerulosclerosis in chronic renal failure.[31,95] Studies have shown that lipid lowering may have a beneficial effect on renal function.[96] A meta-analysis of 13 controlled trials involving a total of 362 subjects, 253 of whom had diabetes, showed that statins decreased proteinuria and preserved GFR in patients with chronic renal disease.[97] These effects could not be

entirely explained by a reduction in blood cholesterol. Adequately powered randomized controlled trials will be needed to determine the role of lipid-lowering therapy in retarding the rate of decline in kidney function in patients with chronic renal disease secondary to diabetes mellitus.

Multifactorial Approach

Experimental and clinical studies have shown that the optimal therapeutic approach in the treatment of DN may be intensive combined therapy targeting hyperglycemia, hypertension, microalbuminuria, and dyslipidemia.[98,99] The Steno Type-2 Study compared an intensive multifactorial intervention to standard therapy in 160 patients with type-2 diabetes.[98] There was 73% reduction in the incidence of clinical proteinuria in the multifactorial intervention group. In addition, the intensive therapy was also more effective in lowering HbA_{1c} values (7.6% vs. 9.0%), fasting plasma glucose (134 vs. 185 mg/dL [7.4 vs. 10.2 mmol/L]), LDL cholesterol (112 vs. 127 mg /dL [2.9 vs. 3.3 mmol /L]), systolic BP (138 vs. 145 mmHg) and the rate of progression of retinopathy and autonomic neuropathy.

Potential Therapeutic Option

Use of Glycosaminoglycans

Glycosaminoglycans have been shown in experimental and clinical studies to prevent diabetes-induced albuminuria, loss of anionic sites, thickening of the glomerular basement membrane, and glomerulosclerosis.[100,101] The Diabetic Nephropathy and Albuminuria Sulodexide (DiNAS) study was a randomized, double-blind, placebo-controlled, multicenter, dose-finding trial to evaluate the extent and duration of the hypoalbuminuric effect of oral sulodexide (containing two glycosaminoglycans) in patients with diabetes.[102] Sulodexide significantly and dose-dependently improves albuminuria in type-1 and type-2 diabetes.[102] Glycosaminoglycans are yet to be approved by the Food and Drug Administration in DN.

Renal Replacement Therapy

The renal replacement modalities available for patients with ESRD from diabetes include peritoneal dialysis, hemodialysis, and renal transplantation. Various studies have shown similar survival in hemodialysis and peritoneal dialysis, though patients are more likely to persist with hemodialysis than with peritoneal dialysis.[103] Both hemo- and peritoneal dialysis limit social life, leisure, and sexual activity.[104] Patients with diabetes may manifest uremic symptoms at a relatively less-advanced degree of renal insufficiency than their nondiabetic counterparts.[105]

The choice of a dialysis modality in patients with diabetes depends on the following factors: comorbid conditions, home situation, ability to tolerate volume shifts, independence and motivation of the patient, state of the vasculature and/or abdomen, and the risk and history of infection.[105,106] Hemodialysis has the advantage of being very efficient, and in-center hemodialysis allows frequent medical follow-up and assessment.[103] Diabetic patients with autonomic dysfunction or diastolic dysfunction are more often likely to develop hypotension during hemodialysis due to poor toleration of volume shifts.[103,105] Due to gradual fluid removal in continuous ambulatory peritoneal dialysis, the procedure is not usually associated with hypotension unless the patient is volume-depleted, and it is thus better suited for patients with diabetes. Peripheral vascular disease is common in older patients with type-2 diabetes and this limits the ability to create and sustain adequate vascular access for

Table 3. Multifactorial Approach in the Management of Diabetic Nephropathy

- Control of blood sugar (ADA Targets)
  - Preprandial glucose: 80–120 mg/dL (whole blood); 90–130 mg/dL (plasma)
  - Bedtime glucose: 100–140 mg/dL (whole blood); 110–150 mg /dL (plasma)
  - Glycosylated hemoglobin: <7%
- Control of Blood Pressure (ADA, NKF Targets)
  - <130/80 mm Hg in patients with proteinuria <1 g/day.
  - <125/75 mm Hg in patients with proteinuria ≥1 g/day.
- Control of Blood Lipids (ADA Targets)
  - LDL cholesterol <100 mg/dL (first priority)
  - HDL cholesterol >45 mg/dL (second priority)
  - Triglycerides <200 mg/dL (second priority)

ADA—American Diabetes Association; NKF—National Kidney Foundation

HD.[105] In patients with diabetes, survival rates of both arteriovenous fistulae and grafts are substantially reduced.[106] In visually impaired patients with diabetes, continuous cycler-assisted continuous peritoneal dialysis is a good choice since it requires the performance of only one "on" and one "off" procedure daily.[107] In patients with diabetes, intraperitoneal administration of insulin gives better control of blood sugar, thereby reducing the incidence and the severity of hypoglycemic episodes. However, glycemic control may be deranged following long-term peritoneal dialysis due to the large amount of glucose administered in dialysis solution.

Mortality and morbidity are substantially higher in patients with diabetes maintained on dialysis than in their nondiabetic counterparts with cardiovascular disease and infections being the leading causes of death. Survival on dialysis is influenced by factors, such as age, adequacy of dialysis, and nutritional status. Survival varies inversely with age, being best in young patients with good blood pressure control and no clinically evident cardiac disease. Patients with diabetes are more sensitive to inadequate dialysis prescription, and it is estimated that there is a 7% increase in mortality in patients with diabetes for every 0.1 unit decline in fractional urea clearance [Kt /V].[108] Survival is also affected adversely by malnutrition. Factors contributing to malnutrition in diabetes include inadequate food intake, diabetic gastroparesis and enteropathy, and the catabolic stress associated with frequent intercurrent illness.[105]

Renal transplantation is associated with better survival, improved quality of life, and a higher degree of rehabilitation compared to dialysis. Subset analysis of data on nearly 230,000 dialysis patients, of whom almost 45% were diabetic, found that 7,200 diabetic transplant recipients had significantly lower relative risk of death 18 months after transplantation, compared with approximately 15,000 diabetic waiting-list patients on dialysis (0.27, $p<0.001$).[109] Some of the benefits associated with renal transplantation derive from selection of younger patients with no cardiac diseases. Recurrence of DN can occur in the allografts. This occurs as a result of poor glycemic control and/or insulin deficiency. Offering the patient with type-1 diabetes combined pancreas-kidney transplantation can prevent recurrence of DN.

Pancreas-kidney transplantation may be in the form of simultaneous pancreas-kidney transplantation or sequential pancreas after kidney transplantation.[110] While simultaneous pancreas-kidney transplantation employs grafts harvested from a single cadaveric donor, sequential pancreas after kidney transplantation typically involves transplantation of a cadaveric pancreas graft into a recipient with a functioning living related or cadaveric kidney allografts. The benefits of combined pancreas-kidney transplantation include improved quality of life due to freedom from both insulin therapy and dialysis, prevention of progression and perhaps partial reversal of microvascular complications as a result of normalization of blood glucose and glycosylated hemoglobin levels, and prevention of recurrence of DN in the allografts and improvement in the lipid profile (fall in serum triglyceride and low-density lipoprotein cholesterol and a rise in high-density lipoprotein cholesterol concentration).[110] In addition, there is improvement in glucagon and epinephrine (adrenaline) responses to hypoglycemia, which results in enhanced perception of hypoglycemic symptoms at higher glucose concentrations. Compared with renal transplantation alone, simultaneous pancreas-kidney transplantation is associated with a significant increase in the risk of deep vein thrombosis and pulmonary thromboembolism.[111] However, the overall survival was not significantly better.

PREVENTION OF DN

Efforts at preventing DN should be at the primary, secondary, and tertiary levels. Primary prevention aims at preventing diabetes in the population. Lifestyle modifications that have been shown to prevent or delay the development of diabetes include regular physical exercise and weight control.[112-114] Exercise also reduces percentage of total and abdominal fat, improves blood lipid levels and insulin sensitivity, decreases blood pressure, and improves endothelial vasodilator function and left ventricular diastolic function.[115] Pharmacologic interventions using glucose-lowering drugs in high-risk individuals have also been reported to cause a significant lowering of the incidence of diabetes.[114] However, when compared with lifestyle interventions, drug therapy was less efficacious and was associated with significant adverse side-effects.[114] Presently, there is insufficient evidence to support the routine use of drug therapy for primary prevention.[116]

Secondary prevention entails strict control of blood glucose, lipids, and blood pressure levels. Tertiary prevention involves screening for proteinuria and instituting appropriate treatment.

CONCLUSION

DN remains the leading cause of ESRD in developed countries, and its prevalence seems to be increasing in the developing countries. The cost of treating this condition, particularly when patients require renal replacement therapy, is enormous. In order to achieve the Healthy People 2010 goal of 78 diabetic persons with new cases of ESRD per million population,[117] a multifactorial approach targeting strict control of blood sugar, lipids, and blood

pressure and use of ACEIs and ARBs in proteinuric patients will be preferable. In addition, low-cost community-based programs to increase physical activity and avoid unhealthy lifestyle choices should be encouraged, since this will lead to reduction in the incidence of diabetes in the populace.[116]

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